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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/202,984	CZERNILOFSKY ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61,63-90 and 92-126* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61,63-90 and 92-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/23/98* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on April 28, 2007 has been entered.

Status of the Application

2. Currently claims 61, 63-90 and 92-126 are pending. Claims 1-60, 62, and 91 are cancelled. Claims 61 and 90 are amended. All arguments and amendment have been fully considered and thoroughly reviewed and deemed persuasive for the reasons that follow. 3. The instant amendment introduces new limitations in the independent claims 61 and 90, that is, "test substances"(in plurality) and step (b) reciting ' applying test substances (plurality of test substances) in parallel to one or more sets of said test cells' (plurality of sets of test cells) which is not present in the previously examined claims. The amendment introduced new limitations as shown above and changed the scope of the independent claims. Now the scope of the independent claims is changed, accordingly the following new combination of rejections has been applied to reject newly presented claims. Applicants' arguments are fully considered and found persuasive for the reasons that follow. This action is made Final, necessitated by Amendment.

New Grounds of Rejections necessitated by amendment

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 61, 67-69, 76, 81-85, 87-90, 96-98, 105, 110-114, 116-126 are rejected under 35 U.S.C. 102(b) as being anticipated by Harpold et al. (WO 92/02639).

Harpold et al. teach high throughput parallel screening method (multiple well -format) of claims 61, 90, of determining the pharmacological effect of test substances on the activity of different biological target molecules (cell surface receptors or ion channels) contained in test cells of same type (transformed cells) or different type (recombinant cells having the same c-fos gene regulatory element) (see page 14, line 1-35, page 15, line 1-35, page 27, line 5-36), comprising

(a) selecting from a cell population test cells of the same type or different type which contain different molecules (selecting clones of transformed cell line having different gene targets (cell surface receptors, (see page 28 to 37, example 1, page 41, line 4-27);

(b) applying from the same supply a defined amount (1.4nM) of test substances (antagonists and agonists) to one or more set of test cells of the same type comprising more than one cellular substrates (receptors), which differ in that they contain different target molecules (different receptors) (see page 38, line 25-36, page 39, line 1-36, example 3, page 41, line 4-27);

(b) measuring the effect of the substance on the biological activities of said different target molecules using a detection system using different assays or assay format for each cellular substrate (see page 40, line 1-36);

(c) directly or indirectly comparing the effect of said test substances on the biological activities of said different target molecules, wherein target molecules comprise receptor-coupled signal transduction pathway (see page 40, table 1, page 41, line 4-27).

With regard to claims 67-69, 76, 96-98, 105, Harpold et al. teach that said different target molecules include signal transductionpathway molecules , such as G-protein coupled receptors, growth factor receptors, serotonin receptors ($5HT_2$, etc. (see page 14, line 13-35, page 22, line 6-32, page 24, line 1-26).

With regard to claim 81-82, 110-111, Harpold et al. et al. teach that said test cells are transformed with DNA operably encoding with different receptor molecules (see page 28 to 37, example 1).

With regard to claim 83-85, 112-114, Harpold et al. teach that the detection system comprises luciferase reporter gene expression system (see page 25, line 27-36, page 26, line 1-9).

With regard to claims 87-89, 116-120, Harpold et al. teach that said test cells comprise human cells , different or same type with different states of cells, tumor and normal cells (see page 28, line 30-36, page 33, line 7-28).

With regard to claims 121-126, Harpold et al. teach that said test cells are clonally selected from a single cell, using antibiotic resistance marker (Amp^r) (see page 31, line 2-9). Accordingly Harpold et al. anticipates the instant claims.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 63-64, 66, 70-71, 74-75, 77-80, 92-93, 95, 99-100, 103-104, 106-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harpold et al. (WO 92/02639) in view of Johnson (WO95/28421).

Harpold et al. teach a highthrough-put parallel method of determining the pharmacological effects of test substances as discussed above in section 4.

However, Harpold et al. did not teach target molecules comprising Ras, Raf, receptors as EGF, biological activity comprising proliferation, apoptosis, cells with different states of differentiation or activation.

Johnson teaches a method of determining the pharmacological effect of a substance (test substance) on the activity of different biological target molecules in the signal transduction pathway wherein said different target molecules, wherein target molecules comprise receptor-coupled signal transduction pathway (see page 61, line 16-28, page 62, line 1-22); said different target molecules include Ras, Raf, tyrosine kinase receptors serotonin receptors, human growth hormone receptors, neurokinin receptors 1,2 (tachykinin receptors) EGF etc. (see page 5, line 1-

9, page 17, line 1-16); said biological activity is a pathological effect including proliferation, or apoptosis (see page 6, line 9-24, page 18, line 21-28, page 19, line 1-28, page 20, line 1-28).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Harpold et al. with various signaling molecules that control cell differentiation/ growth/ apoptosis as taught by Johnson to achieve an improved method in evaluating the effect of a substance on the regulation of signal transduction pathway dependent cell differentiation / cell death or apoptosis because Johnson explicitly taught that the growth and differentiation are tightly regulated by signal transduction pathways within cells, which maintain the balanced steady state functioning of a cell and any break down in the signal transduction in a cell would lead to disease states that disturb the cellular functions (see page 6, line 9-24). An ordinary practitioner would have a reasonable expectation of success that the combination of method of Harpold et al. with target molecules of signal transduction pathway as taught by Johnson would result in evaluating the effect of a substance on the signal transduction pathway that directs the growth and differentiation within a cell and such a modification of the method is considered as obvious over the cited prior art.

B. Claims 65, 72-73, 94, 101-102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harpold et al. (WO 92/02639) in view of Johnson (WO 95/28421) as applied to claims 63-64, 66, 70-71, 74-75, 77-80, 92-93, 95, 99-100, 103-104, 106-109 above, and further in view of. Bischoff et al. (USPN. 5,705,342) and Brown et al. (USPN. 5,929,081).

Harpold et al. in view of Johnson teach a high throughput parallel screening method as discussed in section 5A above.

However neither Harpold et al. nor Johnson teach the target molecules as Bcl-2, receptors as HER2, and KDR.

Bischoff et al. et al. teach regulation of cell proliferation control and neoplasia by Bcl-2 expression (see col. 3, line 2-48) and the signal transduction mediated by the association between Ras and bcl-2 (see col. 8, line 49-67).

Brown et al. teach method for treating diseases mediated by cellular proliferation signal transduction pathway effector molecules, wherein Brown et al. disclose that the method comprises treating the diseases associated with cellular target receptor molecules such as VGEF (kinin domain receptors (KDR)), HER2, 3, ras/Raf pathway signaling molecules (see col. 10, line 13-58).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Harpold et al. in view of Johnson with target molecules comprising Bcl-2 as taught by Bischoff et al. and receptors as HGF, HER2 and KDR as taught by Brown et al. to enhance the sensitivity of the method to detect the signaling pathway as a whole because Bischoff et al explicitly taught the meadiation of Ras in controlling bcl-2 function that regulates cell proliferation and neoplasia (see col. 3, line 2-48, col. 8, line 49-67). Further Brown et al. explicitly taught treating diseases mediated by cellular proliferation signal transduction pathway effector molecules, wherein Brown et al. disclose that the method comprises treating the diseases associated with cellular target receptor molecules such as VGEF (kinin domain receptors (KDR)), HER2, 3, ras/Raf pathway signaling molecules (see col. 10, line 13-58). An ordinary practitioner would have been motivated to combine the method of Harpold et al. in view of Johnson with Bcl-2 target molecule and receptors as HGF, HER2 and KDR as

taught by Brown et because an ordinary practitioner would have a reasonable expectation of success that the inclusion of various signal transduction pathway mediators would result in an enhanced method for determining the effect of a substance on the regulation of signal transduction that controls the cell differentiation and apoptosis and such a modification of the method is considered obvious over the cited prior art.

C. Claims 86, 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harpold et al. (WO 92/02639) in view of Chalfie et al. (USPN.5,491,084).

Harpold et al a high throughput parallel screening method as discussed in the section 4 above. Harpold et al. did not teach green fluorescent protein as a reporter gene.

Chalfie et al. teach a method for cells expressing a biological activity (gene expression) of a particular target molecule, wherein the regulatory sequences of a target molecule are linked to a reporter fluorescent protein which fluoresces when said target is expressed within the cells (see column 1, lines 38-52). Chalfie et al. also teach that said reporter fluorescent protein is a gene encoding a green fluorescent protein (column 1, lines 38-41).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of determining the effect of a substance on the biological activities on target molecules as taught by Harpold et al. with the method of detecting effect of a substance on different target molecules linked to a GFP reporter gene system as taught by Chalfie et al. to achieve an enhanced sensitivity in determining the effect of a substance on the biological activity or activities because Chalfie et al. taught that the biological activity of a particular target molecule in response to an external stimulus can be monitored within the cells containing the target by the expression of green fluorescence protein linked to said target and the

cells expressing the GFP can be easily selected and sorted by a fluorescent-activated sorter (see column 4, lines 3-12). Therefore an ordinary practitioner would have a reasonable expectation of success that the combination of the reporter gene mediated detection method of determining the effect of a substance on the biological activity as taught by Harpold et al. with the method of selecting or localizing a biological activity within the cells using the reporter gene encoding a green fluorescent protein as taught by Chalfie et al. would result in enhance the detection of the biological activity of a target molecule within the cells, so as to detect and sort the cells expressing the target molecules without lysing the cells and such modification of the method is obvious over the cited prior art.

Response to arguments:

6. With regard to the rejection of the claims under 35 USC 102(b) as being anticipated by Weyer et al. , Applicants' amendment and arguments are fully considered and found persuasive. The rejection is withdrawn herein in view of the amendment.

7. With regard to the rejection of the claims under 35 USC 103(a) as being obvious over Weyer et al. in view of Johnson, Applicants' amendment and arguments are fully considered and found persuasive. The rejection is withdrawn herein in view of the amendment.

8. With regard to the rejection of the claims under 35 USC 103(a) as being obvious over Weyer et al. in view of Johnson, further in view of Bischoff and Brown Applicants' amendment and arguments are fully considered and found persuasive. The rejection is withdrawn herein in view of the amendment.

9. With regard to the rejection of the claims under 35 USC 103(a) as being obvious over Weyer et al. in view of Chalfie, Applicants' amendment and arguments are fully considered and found persuasive. The rejection is withdrawn herein in view of the amendment.

10. With regard to the rejection of the claims under 35 USC 103(a) as being obvious over Weyer et al. in view of Johnson, further in view of Chalfie, Applicants' amendment and arguments are fully considered and found persuasive. The rejection is withdrawn herein in view of the amendment.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suryaprabha Chunduru
Primary Examiner
Art Unit 1637

Prabha Chunduru 7/5/07
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